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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,282	06/18/2001	Bonnie M Davis	U013469-7	6731

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,282	DAVIS, BONNIE M	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-22,24-26 and 28-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-22,24-26 and 28-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/14/04; 2/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1, 3-5, 7-22, 24-26, and 28-40 are pending.

2. Claims 1, 3-5, 7-22, 24-26, and 28-40 are rejected.

Response to Arguments

3. Applicant's arguments filed January 14, 2004 have been fully considered but they are not persuasive. Applicant presents the following arguments. First, applicant alleges hindsight was used in arriving at the instant rejections. Second, applicant argues that a reference must be considered for what it would teach someone skilled in the art at the time of the invention was made and not be applied based on hindsight. Third, applicant purports that there is no combination of these prior art references, which suggest a formulation of an acetyl cholinesterase inhibitor having a half-life of from one to eleven hours wherein the acetyl cholinesterase inhibitor is formulated so as to delay its activity for a predetermined period form four to twelve hours. Fourth, applicant also argues that different drugs are taught in Conte et al. Fifth, applicant further alleges that the instant invention is not concerned with the time of delivery of an acetyl cholinesterase inhibitor, as is the prior art reference of Conte et al.

4. First, applicant alleges hindsight was used in arriving at the instant rejections. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning.

But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Accordingly, the skilled artisan is provided with sufficient teachings and motivation to arrive at the instantly claimed invention in view of the prior art rejections of Shapiro et al. in view of Conte et al. as well as Brossi et al. in view of Conte et al.

5. Second, applicant argues that a reference must be considered for what it would teach someone skilled in the art at the time of the invention was made and not be applied based on hindsight. The references of Shapiro et al. in view of Conte et al. as well as Brossi et al. in view of Conte et al. are all published before the filing date of the instant invention. For this reason, one having ordinary skill in the art is provided with the necessary teachings to develop pharmaceutical agents, namely acetyl cholinesterase inhibitors, at the time the invention was made, and even before the time of applicant's filing date.

6. Third, applicant purports that there is no combination of these prior art references, which suggest a formulation of an acetyl cholinesterase inhibitor having a half-life of from one to eleven hours wherein the acetyl cholinesterase inhibitor is formulated so as to delay its activity for a predetermined period form four to twelve hours. The instant rejections of Shapiro et al. in view of Conte et al. as well as Brossi et al. in view of Conte et al. clearly provide the skilled artisan at, and even before, the instant invention was made with the necessary motivation to utilize pharmaceuticals,

namely acetyl cholinesterase inhibitors, in a variety of modes and methods of administration. In particular, Conte et al. teach one having ordinary skill in the art to develop and employ controlled- or extended-release forms of pharmaceuticals. In view of these teachings, the skilled artisan is provided with ample motivation to make pharmaceuticals, like acetyl cholinesterase inhibitors, in delayed-release formulations.

7. Fourth, applicant also argues that different drugs are taught in Conte et al. This argument is not found persuasive because the intent of Conte et al. is to teach artisans of delayed-release formulations of pharmaceuticals that are to be administered at certain times in order to have beneficial effects.

8. Fifth, applicant further alleges that the instant invention is not concerned with the time of delivery of an acetyl cholinesterase inhibitor, as is the prior art reference of Conte et al. Applicant eve argues that Alzheimer's disease does not have diurnal variation and treatment is not controlled by circadian rhythm. Conte et al. undisputedly teach of formulating delayed-release pharmaceuticals for a variety of reasons. Conte et al. disclose that there is a need to administer pharmaceuticals in forms that release the drug both at the best possible rate and at the best possible time, (see column 2, page 1017). In summary, the skilled artisan is provided with motivation and explicit teachings to make pharmaceuticals, such as those of Shapiro et al. and Brossi et al., for the treatment of Alzheimer's disease in a delayed-release formulation.

Information Disclosure Statement

9. The information disclosure statements filed on January 14, 2004 and February 9, 2004 have been reviewed and considered, see enclosed copies of PTO FORMS 1449.

Claim Rejections - 35 USC § 112

10. The rejection of claims 1, 3-5, 21, 22, 24-26, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained because the prior art does not teach that all of these inhibitors of acetyl cholinesterase possess these types of properties, see Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, pgs 161-176, Chapter 8, 1996. In fact, some of these inhibitors of acetyl cholinesterase, such as the organophosphorus compounds, like sarin, or even pralidoxime, are not used therapeutically to treat Alzheimer's disease.

11. The rejection of claims 21, 24-26, and 28-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained because the prior art teaches the compounds of the inventions are acetyl cholinesterase inhibitors. However, the prior art does not teach that all of these inhibitors of acetyl cholinesterase possess these types of properties, see Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, pgs 161-176, Chapter 8, 1996. In fact, some of these inhibitors of acetyl cholinesterase, such as the organophosphorus compounds, like sarin, are not used therapeutically to treat Alzheimer's disease.

12. The rejection of claims 3, 4, 24, and 25 is withdrawn in view of the amendment of January 14, 2004.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1, 3-5, 21, 22, 24-26, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the acetyl cholinesterase inhibitors of galanthamine, lycoramine, and rivastigmine, does not reasonably provide enablement for other types of acetyl cholinesterase inhibitors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use and make the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to pharmaceutical compositions of acetyl cholinesterase inhibitors.

(2) The state of the prior art

The compounds of the inventions are acetyl cholinesterase inhibitors. However, the prior art does not teach that all of these inhibitors of acetyl cholinesterase possess these types of properties, see Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, pgs 161-176, Chapter 8, 1996. In fact, some of these inhibitors of acetyl cholinesterase, such as the organophosphorus compounds, like sarin, are not used therapeutically to treat Alzheimer's disease.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements functioning the same in different circumstances, yielding predictable results, but chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24

(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of acetyl cholinesterase inhibitors prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to the plethora of compounds embraced by the functional recitation of being known as acetyl cholinesterase inhibitors. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein

and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of acetyl cholinesterase inhibitors to be effective in treating any disease or condition in which it is desirable to administer an acetyl cholinesterase inhibitor is insufficient for enablement. The specification provides no guidance, in the way of enablement for acetyl cholinesterase inhibitors other than the acetyl cholinesterase inhibitors of galanthamine, lycoramine, and rivastigmine. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and

electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Accordingly, this is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds that fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses the acetyl cholinesterase inhibitors of galanthamine, lycoramine, and rivastigmine that have the ability to treat any disease or condition in which it is desirable to administer an acetyl cholinesterase inhibitor. However, the instant specification only has enablement for the acetyl cholinesterase inhibitors of galanthamine, lycoramine, and rivastigmine.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the inhibitors of acetyl cholinesterase that would be enabled in this specification.

Claim Rejections - 35 USC § 103

15. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. The rejection of claims 1, 3-5, 7-21, 22, 24-26, 28-38 under 35 U.S.C. 103(a) as being unpatentable over Shapiro et al. in view of Conte et al. is maintained for both the reasons of above and of record. In addition, the rejection of Shapiro et al. in view of Conte is restated.

17. Shapiro et al. provide the necessary disclosure to the skilled artisan for a clinical treatment method of Alzheimer's disease with the administration of the acetyl

cholinesterase inhibitor of galanthamine, (see column 30, lines 28-32 and column 32, lines 21 and 55-57). In addition, it would have been obvious to the skilled artisan to include or utilize other types of acetyl cholinesterase inhibitors, which would obviously embrace rivastigmine and lycoramine, in pharmaceutical preparations an also with the treatment of Alzheimer's disease. Moreover, Shapiro et al. is directed to the clinical treatment of neurodegenerative diseases, which includes Alzheimer's disease, (see column 1, lines 22-29).

18. The rejection of claims 1, 3-5, 21, 22, 24-26 under 35 U.S.C. 103(a) as being unpatentable over Brossi et al. in view of Conte et al. is maintained for both the reasons of above and of record. The rejection of Brossi et al. in view of Conte et al. will follow. First, the prior art reference of Brossi et al. pertains to the administration of acetyl cholinesterase inhibitors. However, instant claims 1, 3-5, 21, 22, 24-26 are only directed to the administration of an acetyl cholinesterase inhibitor. In addition, Brossi et al. teach that anticholinesterase inhibitors are useful in the treatment of Alzheimer's disease, (see column 1, lines 13-17). Brossi et al. teach of various pharmaceutical excipients, preparations and dosages of these acetyl cholinesterase inhibitors, (see columns 8-10).

19. Next, the prior art references of Shapiro et al. and Brossi et al. are combined with Conte et al. in order to reject the instantly claimed invention. Conte et al. provide the skilled artisan with the motivation that there is a need in the art for the rate-controlled delivery of medication, (see columns 1 and 2 on page 1017). Conte et al. also teach that "[i]t is well known that a drug must be given in the right dosage to

produce the desirable effect, but the rate at which the active ingredient is administered/absorbed is also very important for its therapeutic effect." In addition, Conte et al. disclose there is an increasing awareness that the drug must be administered not only in the right amount at a proper rate but also at the right time, (see column 1, page 1017). Conte et al. also disclose of a proper need in time-programmed release of drugs that are related to changes in the alternation between day and night (activity and rest). Conte et al. further state that there is a need to administer pharmaceuticals in forms that release the drug both at the best possible rate and at the best possible time. In fact, Conte et al. specifically teach the artisan of pharmaceuticals that, "are able to release a drug at a specific rate, but the release starts only after a well defined period of time, (as cited from column 2, page 1017). It could not be more clear from the teachings of Conte et al. that one having ordinary skill in the art is provided not only with the motivation but with explicit disclosures to make and prepare pharmaceuticals in a delayed-release or time-programmed release forms. Accordingly, the skilled artisan is provided with the necessary information to generate pharmaceuticals, such as those disclosed in Shapiro et al. and Brossi et al., for the treatment of Alzheimer's disease in a delayed-release or time-programmed release form as clearly taught by the prior art reference of Conte et al. It would have been obvious to one having ordinary skill in the art to employ acetyl cholinesterase inhibitors, namely galanthamine, to treat Alzheimer's disease as taught by both Shapiro et al. and Brossi et al. Moreover, the skilled artisan is provided with the necessary motivation and teachings of Conte et al. to prepare pharmaceuticals in a delayed-release or time-

programmed release forms, especially when the release of drugs at the best possible time that is related to changes in the alternation between day and night (activity and rest), as directly cited from Conte et al.

Obviousness-type Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1, 3-5, 7-22, 24-26, and 28-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-40 of copending Application No. 10/397,682. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant invention and copending Application No. 10/397,682 teach of sustained-release pharmaceuticals of acetyl cholinesterase inhibitors as well as employing these pharmaceuticals for the treatment of Alzheimer's disease.

22. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584. The official fax No. for correspondence is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
May 1, 2004